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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/659,578	09/10/2003	Zsuzsanna Nagy	43962-010810	4669

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EXAMINER	
BURKHART, MICHAEL D	
ART UNIT	**PAPER NUMBER**
1633	

MAIL DATE	DELIVERY MODE
10/18/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/659,578	NAGY, ZSUZSANNA	
	Examiner	Art Unit	
	Michael D. Burkhart	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 August 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-3,5-17 and 30-40* is/are pending in the application.

4a) Of the above claim(s) *7,9-16,33 and 35-40* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3, 5, 6, 8, 17, 30-32, and 34* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Receipt and entry of the amendment dated 8/6/2007 is acknowledged. After entry of the amendment, claims 1-3, 5-17 and 30-40 are pending and under examination. Claims 7 and 9-16 remain withdrawn as being drawn to nonelected inventions, there being no allowable generic or linking claim. New claims 33 and 35-40 are withdrawn for reasons set forth below. Claims 1-3, 5, 6, 8, 17, 30-32, and 34, i.e. Group II as set forth in the restriction requirement dated 9/19/2006, are under examination.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office Action.

Election/Restrictions

Newly submitted claims 33 and 35-40 are directed to inventions that are independent or distinct from the invention originally claimed for the following reasons: as pointed out by applicants, claims 33 and 35-40 are encompassed by non-elected Groups I and III-VII, as set forth in the restriction requirement dated 9/19/2006.

Since applicant has received an action on the merits for the originally presented invention, this invention has been constructively elected by original presentation for prosecution on the merits. Accordingly, claims 33 and 35-40 are withdrawn from consideration as being directed to non-elected inventions. See 37 CFR 1.142(b) and MPEP § 821.03.

Specification

The specification is objected to as failing to provide proper antecedent basis for the claimed subject matter. See 37 CFR 1.75(d)(1) and MPEP § 608.01(o). Correction of the

following is required: the term "cell division G1 inhibitor substance", e.g. as recited in claims 3 and 8 is not found within the specification.

Claim Rejections - 35 USC § 112

Claims 1-3, 5, 6, 8, 17, 30-32, and 34 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. **This is a new rejection necessitated by applicants' amendment of the claims in the response filed 8/6/2007. This is a New Matter rejection.**

Amended claim 1 (from which all other claims depend) recites, in part (B), a step of comparing a determined G1/S cell cycle checkpoint effectiveness with "the G1/S cell cycle checkpoint effectiveness exhibited by...an individual having said neurological condition". The response indicates support for the amendment may be found in the paragraph bridging pages 3-6, 9, 10 and 23-30. These passages do not recite a step of comparing the determined G1/S effectiveness with that of "an individual having said neurological condition". Rather, a review of the specification and claims as originally filed discloses that the determined G1/S effectiveness of the subject is to be compared to control cells from either healthy patients, or to cells that do not have a cell cycle regulatory defect. Therefore, there appears to be no support for the method step of comparing a determined G1/S cell cycle checkpoint effectiveness with "the G1/S cell cycle checkpoint effectiveness exhibited by...an individual having said neurological condition". Thus, the amended claims include impermissible New Matter.

Claims 1-3, 5, 6, 8, 17, 30-32, and 34 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. **This rejection is maintained for reasons set forth in the Office Actions dated 7/21/2005, 3/6/2007, and for reasons set forth below. New claims have been added due to amendment of the claims**

Response to Arguments

Applicant's arguments filed 8/6/2007 have been fully considered but they are not persuasive. Applicants essentially assert that: 1) the declaration by Dr. Nagy (the Nagy Declaration) indicates the claimed methods are at least as useful, reliable, and specific as current methods, e.g. the NINCDS-ARDRA criteria; 2) a patented invention need not be the best way to accomplish a goal; 3) the data from the instant application do not contradict that found in Nagy et al (2002); 4) the Nagy declaration addresses the misdiagnosis of cancer patients by the instant methods, primarily because non-cancerous cells would not be tested; 5) the Nagy declaration addresses the ability of ionizing and UV radiation to arrest cells in G1; 6) an analysis of the Wands criteria indicates that the claimed invention is enabled; 7) the Examiner is incorrect in stating the breadth of the claims can include an increase in the effectiveness of the G1/S checkpoint, as such an increase is not possible due to the nature of the checkpoint itself.

Regarding 1) and 2), the Examiner has never maintained that the claimed invention is not useful, i.e. this is not a utility rejection. Furthermore, a review of the enablement rejection set forth in the previous Office Action does not find any allegation that the claims are so rejected because they are not the "best" way to accomplish the claimed method.

Regarding 1) and 3), the Nagy declaration compares different data than that alleged by the Examiner to be "unreliable". The Nagy declaration compares two sets of so-called "relative" G1 lengthening data, i.e. Fig. 1A from the Nagy et al and the left-hand chart from Fig. 2 of the application, both of which appear to have not been age-corrected (there is no mention of age-correction in Nagy et al 2002). The Examiner agrees that these graphs are similar, but this misses the point set forth in the previous Office Action on two important grounds: 1) ample evidence that only age-corrected data should be used in Alzheimer's disease (AD) diagnosis has been presented in the previous Office Actions (e.g. see page 5 of the 7/21/2005 Office Action), this is because without such correction, any differences seen in experimental data may be due to age differences between the controls and subjects, not a difference due to the subject having AD; 2) the claims are not limited to any manipulation of the data regarding age-correction, hence, they encompass both situations set forth in Fig. 2 of the instant specification. If one compares these graphs (or to Fig. 1A in Nagy et al 2002), as set forth in the previous Office Action, one draws several different conclusions, in firm support of the Examiners conclusions of unreliability and the inability of the instant method to diagnose AD commensurate in scope with the claims. To review, a strict reading of the claims in light of the data set forth in Fig 1A of Nagy et al (2002) and the left hand graph of the instant Fig. 2 leads to the incorrect diagnosis of the DNOS group as having AD, and possibly would not lead to the diagnosis of members of the possAD

group as having AD (i.e. see the error bars of the possAD group in Fig. 2, left hand graph). Already the method has created false positives in three DNOS subjects (Table 1a of the specification) and an unknown number of false negatives in the possAD group, and this does not even take into account errors introduced by not applying age correction, the large number of false negatives known to be missed by current methods of AD diagnosis, and the number of false positives introduced by the testing of cancerous cells with a G1/S defect.

On the other hand, a strict reading of the claims in light of the data set forth in Fig 1A of Nagy et al (2002) and the right hand graph of the instant Fig. 2 leads to different diagnosis of the possAD, ADM, and DNOS groups. This is the basis for the unreliability set forth in the previous Office Action, i.e. depending on how the data are manipulated, opposing results are generated for the same subjects. According to the teachings of the prior art, the right hand graph of Fig. 2 (age-corrected) should be used. Doing so would improve the misdiagnoses of the DNOS group as having AD when the left hand graph is used, but aggravates the situation with the false negative diagnosis of the possAD group and introduces questionability as to which individuals in the ADM group should be diagnosed with AD, if any. Table 1a of the specification indicates the possAD group had 3 subjects and the ADM group 7 subjects, out of a total of 35 subjects and 14 controls. If the 10 members of the ADM and possAD groups were misdiagnosed, the assay is only 71% accurate. This number does not take into account the problems set forth above, i.e. the known false negative rate inherent to AD diagnoses methods, and the false positives generated by testing cancerous cells. Furthermore, in this respect, the instant methods are less sensitive and reliable than the NINCDS criteria, which did diagnose the possAD and ADM groups.

Regarding 4), it is noted that the features upon which applicant relies (i.e., testing non-cancerous cells, performing other diagnostic steps, testing cells from elderly individuals only) are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993). The claims remain extremely broad, and read on testing any non-neuronal cells, including lymphocytes, which are specifically recited (claim 17), from any human subject, regardless of age, health, etc. Thus, the claims encompass testing cells from patients that may or may not have cancer, and specifically lymphocytes from such a patient. Absent evidence to the contrary, and as only a limited example of non-neuronal cells, leukemia or lymphatic cancer cells would be found in this group of cells. The fact remains that cancerous cells with a G1/S defect, as exemplified by the rapamycin resistant cells taught in the art of record, would give a false positive result in the claimed methods.

Regarding 5), the effects of UV and ionizing radiation are not specific to G1 or G1/S, which was the point of the argument. The instant application does not teach how to practice the claimed methods, i.e. assaying for a specific block in the G1/S transition, using stimuli that induce arrest throughout the cell cycle, i.e. stimuli that are not specific to G1/S. See the teachings of Callegari et al (2006) and Houtgraaf et al (2006), which document that UV and ionizing radiation induce cell cycle arrest in G1/S, S and G2/M. Lengthening of the S and G2/M phases by this arrest would give spurious results in the assay set forth in the specification to measure G1 lengthening, i.e. BrdU incorporation followed by FACS analysis.

Regarding 6), the analysis of the Wands factors presented in the previous Office Action stands. It was not alleged that the skilled artisan could not perform routine assays, such as FACS

or diagnostic molecular biology, nor that they were laborious. The relevant point is that the specification requires the skilled artisan to practice laborious trial and error experimentation to develop a reliable and effective assay that differentiates AD from other dementias and cancer by merely assaying for a G1/S checkpoint defect, i.e. the claimed invention. Again, the Examiner has never alleged that routine assays associated with the claimed invention are not enabled.

The disclosed working examples, and pages 23-30 as indicated by applicants, use the NINCDS-ARDRA criteria to compare the G1/S experimental data. The indicated passages of the specification only indicate the experiments were done blind, whereas the comparison (i.e. step (B) of claim 1) was done in conjunction with the already determined NINCDS-ARDRA criteria. Thus, the working examples relied upon the NINCDS-ARDRA criteria to classify the patient/subject samples.

Regarding applicants assertions that the claimed scope is enabled, the analysis of the claimed scope stands. The claims are broad in nature and read on diagnosing AD by merely assaying for a G1/S checkpoint defect in any non-neuronal cell, in any human subject, which could be a reduction in effectiveness of the checkpoint (i.e. as in claim 3), or an increase in the effectiveness of the checkpoint (within the scope of claim 1).

Regarding 7), this argument is untrue on its face. A reading of the specification and the data set forth in Fig. 2 teaches that variance in the length of the G1/S checkpoint can either be less than or greater than (i.e. an increase in the effectiveness of the checkpoint) a given control or starting point. See Fig. 2, left hand graph, as one example wherein the possAD group variance sets forth that the length of the G1/S checkpoint was greater, i.e. more effective, relative to controls. Furthermore, the specification provides no link between an increase in G1

effectiveness and diagnosis of AD. Finally, claims 1-2 have not been amended to recite a decreased effectiveness limitation, as applicants indicate on page 14 of the response.

Response to Amendment

The affidavit under 37 CFR 1.132 filed 8/6/2007 is insufficient to overcome the rejection of claims 1-3, 5, 6, 8, 17, 30-32, and 34 based upon insufficiency of disclosure under 35 U.S.C. 112, first paragraph as set forth in the last Office action because: many of the arguments presented in the Nagy declaration are addressed above, to the extent that are not, they are addressed below.

The Nagy declaration essentially asserts that: 1) the 2006 publication has been taken out of context, that the Examiner has held the instant claims to an unreasonably high standard e.g., "100%" accuracy of the methods, that diagnostic assays are useful even if they are not 100% accurate, that the claimed methods have a positive predictive value at least as good as the NINCDS-ARDRA criteria; 2) the testing of cancerous cells would not present a problem in the claimed methods because additional steps are not excluded by the claim language "comprising", such further steps would be used because one skilled in the art would not rely upon a single test to be conclusive, and would use prior training and judgment, along with a patients medical profile.

Regarding 1), the 2006 publication was relied upon to teach that the art of AD diagnosis was, even after applicants filing date, under development and unpredictable. The Examiner never required 100% accuracy of the claimed methods. The instant rejection does not assert that

the claimed methods are not useful, only that they are not enabled, a significant difference covered under distinct, yet in some instances overlapping, statutes. The predictive value of the instant methods appears to be less than the NINCDS-ARDRA criteria for reasons et forth above, e.g. the NINCDS-ARDRA criteria detect possAD and DNOS groups with greater reliability than the instant results would indicate.

Regarding 2) , it is noted that the features upon which applicant relies (i.e., performance of other method steps and diagnostics, use of "judgment" and patient profile, using abnormal blood tests suggestive of cancer, not testing cancerous cells or a tumor biopsy, testing based on longevity of the patient) are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993). As set forth above, the claims are broadly drafted to any human patient and any non-neuronal cell. Arguments that one of skill in the art would know *a priori* what cells and what patients to test are unconvincing given the claimed scope, as are the performance of method steps that are not recited in the claims. Furthermore, the Examiner is unaware of how the skilled practitioner could determine cancerous cells from non-cancerous cells without some kind of test, be it an X-ray, blood test, etc., as the affidavit asserts on page 7. Cancerous cells exist outside of tumors, e.g. tumors metastasize, and cancer exists in non-tumorous forms, e.g. leukemia. Finally, a G1/S defect could exist within a patient without any outside symptoms of cancer because it has become appreciated that cancer is a development of a series of defects in cell growth regulation, e.g. a series of oncogenic mutations which arise over time or are inherited. Thus, a patient may have a resistance to rapamycin due to a G1/S defect, but not necessarily exhibit cancer symptoms

because other mutations have not arisen. See, e.g., Ichimura et al (2000), who teach a G1/S defect is often found in gliomas, but also often requires, *inter alia*, a p53 mutation.

Conclusion

No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Michael D. Burkhart whose telephone number is (571) 272-2915. The examiner can normally be reached on M-F 8AM-5PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach can be reached on (571) 272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Michael D. Burkhart
Examiner
Art Unit 1633

/Joseph Woitach/
Joseph Woitach
SPE 1633